

REMARKS/ARGUMENTS***Status of Claims***

Claims 1, 37, 39, 50, 51, 53, 54, 58-60, 63, and 65 have been amended.

Claims 2-35, 43-49, 55-57, 62, 64, 66 and 67 have been canceled.

Thus, claims 1, 36-42, 50-54, 58-61, 63, and 65 are currently pending in this application.

Applicants hereby request further examination and reconsideration of the presently claimed application.

Claim Rejections – 35 U.S.C. § 112

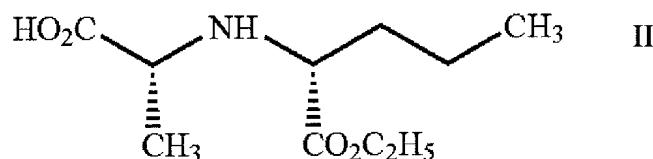
Claims 43, 48, and 64 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 43, 48, and 64 have been canceled.

Claim Rejections – 35 U.S.C. § 103

Claims 1, 36-46, and 48-67 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vincent, et al., U.S. Patent No. 4,914,214 (hereinafter “*Vincent*”). Claims 36-42, 50-54, 58-61, 63, and 65 depend from independent claim 1 and claims 43-46, 48-49, 55-57, 62, 64, 66 and 67 have been canceled. Thus, claims 1, 36-42, 50-54, 58-61, 63, and 65 stand or fall on the application of *Vincent* to the independent claim 1. As noted by the United States Supreme Court in *Graham v. John Deere Co. of Kansas City*, an obviousness determination begins with a finding that **“the prior art as a whole in one form or another contains all” of the elements of the claimed invention.** See *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 22 (U.S. 1966). Applicants respectfully submit that *Vincent* fails to contain all of the elements of independent claim 1. Amended claim 1 recites:

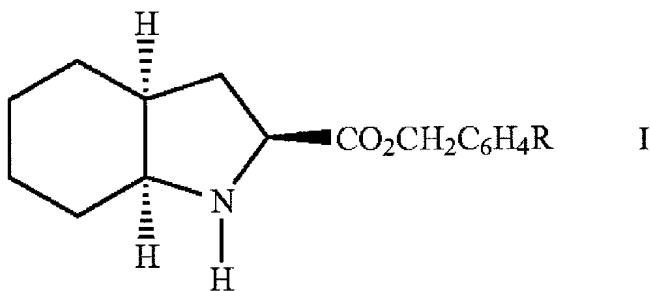
1. A process for preparing perindopril, or a pharmaceutically acceptable salt thereof, which process comprises:

(i) condensation of norvaline ethyl ester with pyruvic acid to yield N-[(S)-1-carbethoxybutyl]- (S)-alanine (II), wherein said condensation is carried out under catalytic hydrogenation at a pressure ranging from 5 to 10 bars and said catalyst and any inorganic salts present in the reaction medium are removed by filtration to obtain a filtrate, the filtrate is concentrated and N-[(S)-1-carbethoxybutyl]- (S)-alanine is isolated by precipitation by the addition of a solvent selected from acetone and ethyl acetate;

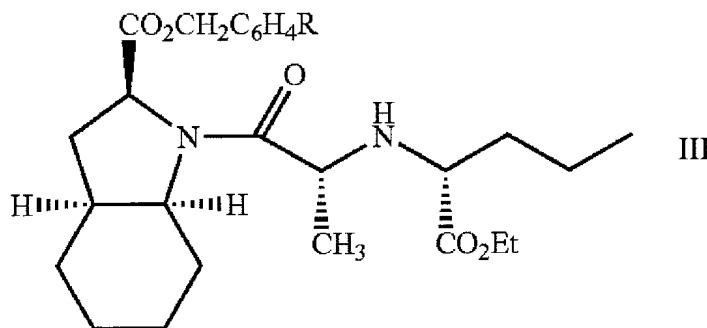


(ii) conversion of an alkali metal salt of S-indoline-2-carboxylic acid to (2S,3aS,7aS)-octahydroindole-2-carboxylic acid by hydrogenation using 5% rhodium on alumina at a pressure of from 5 to 20 bar;

(iii) preparing a substituted benzyl ester of the (2S,3aS,7aS)-octahydroindole-2-carboxylic acid (I), by reaction of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid with the corresponding substituted benzyl alcohol of formula HOCH₂C₆H₄R, wherein either said (2S,3aS,7aS)-octahydroindole-2-carboxylic acid is treated with an excess of the alcohol and thionyl chloride, excess alcohol is distilled off and the residue treated with a solvent to obtain the substituted benzyl ester of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid as a hydrochloride; or said (2S,3aS,7aS)-octahydroindole-2-carboxylic acid is treated with an excess of the alcohol and heated with toluene using a molar quantity of p-toluene sulphonic acid, to obtain the substituted benzyl ester of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid as a salt, and converting the salt to the base, preferably by treatment with ammonia; and



(iv) coupling the substituted benzyl ester of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid (I) from step (iii) with the N-[(S)-carbethoxybutyl]- (S)-alanine (II) from step (i) to form the ester of formula III,



wherein the coupling is carried out in the presence of N,N-dicyclohexyl carbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT)[[:]]; and converting the ester of formula III to perindopril or a pharmaceutically acceptable salt thereof.

See supra (Emphasis added). As shown above, amended claim 1 recites the limitation of *preparing a substituted benzyl ester of the (2S,3aS,7aS)-octahydroindole-2-carboxylic acid.*

Support for the amendment is found in the specification. *See Application at [0010], [0017].*

Vincent teaches only an unsubstituted benzyl ester. *See Vincent col. 8, line 45-col. 9, line 2.*

The Office Action recognizes the inadequacy of *Vincent*, but suggests that:

[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to experiment with the reaction conditions disclosed in *Vincent et al.* (i.e. to test out the hydrogenation reaction at different pressures and to experiment with different protecting groups) in an attempt to find the optimal reaction conditions . . .and to arrive at the process of the instant claims.

Office Action at 4. The Office Action misapplies an “obvious to try” rationale in arriving at the instant rejections. As explained in the MPEP, “an ‘obvious to try’ rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.”

MPEP § 2145 (X)(B) (Emphasis added). To the contrary, the Office Action fails to show that the preparation of *a substituted benzyl ester of the (2S,3aS,7aS)-octahydroindole-2-carboxylic acid* was among a “finite number of identified, predictable solutions.”

Further, the Office Action makes only a conclusory assertion that one of skill in the art would have had a reasonable expectation of success. The Office Action’s blanket assertion runs

contrary to recent precedent by the Federal Circuit, “[t]o the extent an art is *unpredictable as the chemical arts often are . . . potential solutions are less likely to be genuinely predictable.*” *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, 87 USPQ2d 1452 (Fed. Cir. 2008). As such, the Office Action has not presented a *prima facie* case of obviousness.

Further still, the Office Action’s rationale fails because the process of the instant claims yields *more* than predictable results. As explained by the Supreme Court, “[a] rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art.” *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (2007) (Emphasis added). The process described in *Vincent* employs “an excess of p-toluene sulphonic acid This excess of p-toluene sulphonic acid has been found to be detrimental to the purity of the product.” Application at [0005]. As explained in the application, “[the] procedures according to the present invention alleviate the lack of purity associated with the prior art techniques.” Application at [0018]. Because the results attained by operation of the procedures of the instant claim yields results *beyond* what would have been predictable to one of skill in the art, *Vincent* cannot render obvious claims 1, 36-42, 50-54, 58-61, 63, and 65.

Also shown above, amended claim 1 recites the limitation of conversion of an alkali metal salt of S-indoline-2-carboxylic acid to (2S,3aS,7aS)-octahydroindole-2-carboxylic acid by hydrogenation *using 5% rhodium on alumina*. Support for the amendment is found in the specification. See Application at [0022]. To the contrary, *Vincent* teaches only a charcoal support. See *Vincent* at col. 4, lines 28-30; col. 5, lines 49-52. As is commonly acknowledged,

the catalytic arts are inherently unpredictable, and thus blanket conclusions that an alternate compound will produce results similar to those of a prior art compound are insufficient to establish a reasonable expectation of success. Thus, *Vincent* does not contain all of the elements of independent claim 1 and, as such, cannot render obvious claims 1, 36-42, 50-54, 58-61, 63, and 65. Applicants respectfully request withdrawal of the rejections and allowance of the claims.

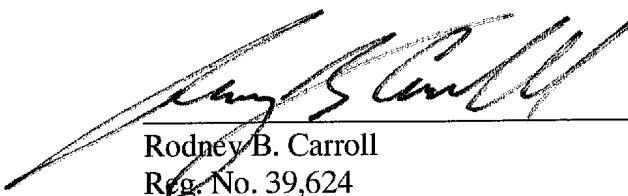
CONCLUSION

Consideration of the foregoing amendments and remarks, reconsideration of the application, and withdrawal of the rejections are respectfully requested by Applicants. No new matter is introduced by way of the amendment. It is believed that each ground of rejection raised in the Office Action dated March 16, 2009 has been fully addressed. If any fee is due as a result of the filing of this paper, please appropriately charge such fee to Deposit Account Number 50-1515 of Conley Rose, P.C., Texas. If a petition for extension of time is necessary in order for this paper to be deemed timely filed, please consider this a petition therefore.

If a telephone conference would facilitate the resolution of any issue or expedite the prosecution of the application, the Examiner is invited to telephone the undersigned at the telephone number given below.

Respectfully submitted,
CONLEY ROSE, P.C.

Date: 6-16-09



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